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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,967	12/31/2001	Wilhelmus Evergardu Hennink	313632001000	8024

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EXAMINER	
FUBARA, BLESSING M	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/913,967	HENNINK ET AL.	
	Examiner	Art Unit	
	BLESSING M. FUBARA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,15-17,24 and 27-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,15-17,24 and 27-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges receipt of request for extension of time, amendment and remarks filed 2/02/2009. Claims 7 and 13 are canceled. Claims 1 and 15 are amended. Claims 1, 15-17, 24 and 27-31 are pending.

Response to Arguments

Previous rejections that are not reiterated herein are withdrawn.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Amended claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. ("Biodegradable brush-like polymers from poly(D, L-lactide) or poly(D, L-lactide-co-glycolide) and charge-modified, hydrophilic dextrans as backbone - synthesis, characterization and in vitro

degradation properties," in *Polymer* **38** (1997), pp. 6197–6206) or Li et al. ("Biodegradable brush-like polymers from poly(D, L-lactide) or poly(D, L -lactide-co-glycolide) and charge-modified, hydrophilic dextrans as backbone -in-vitro degradation and controlled release of hydrophilic macromolecules. *Polymer* **39** (1998), pp. 3087–3097) for reasons of record and modified to address the amendment to the claims.

4. Li in either reference, Vol. 39 or Vol. 38 describes poly D,L lactide grafted dextran (see the entire document with emphasis on the abstract, and experimental section). Li does not disclose that the separate forms, the L-lactide grafted form of dextran and the D-lactide grafted form of dextran are combined to form the composition of claim 1. However, the combination of the L-lactide grafted form and the D-lactide grafted form of dextran reads on the D,L lactide grafted dextran. Specifically, claim 1 does not indicate any special ratios of the L-lactide dextran to the D-lactide dextran that may have provided some difference between the claimed and the disclosed. Regarding the limitation that the lactic acid in the D- or L- forms of the lactic acid has 7-25 lactic acid monomers on the average, it is noted that the artisan has the ability of using lactic acid monomers having appropriate number of lactide monomers that would lead to the desired lactide grafted polymer that would encapsulate and degrade to release hydrophilic molecules. Since the D,L- forms contain the D- and L-forms, one having ordinary skill in the art at the time the invention was made would have reasonable expectation that grafting the dextran with the D,L-form of the lactide or combining the D- or L-lactide grafted forms of the dextran would provide the anticipated in vitro degradation of the polymer or in vitro degradation and controlled releases of hydrophilic molecules such the degradation leads to release of protein or peptides (abstract; pages 3087, 3094, at least). The language of the composition is comprising such that the D,L-lactide grafted form of the dextran meets the L-lactide and D-

lactide grafted dextran. In the absence of unexpected result, a composition that comprises D, L-lactide grafted dextran that is a combination of L-lactide grafted dextran and D-lactide grafted dextran is not inventive over a D,L-lactide grafted dextran.

5. Amended claims 1 and 24 and dependent claims 29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. ("Biodegradable brush-like polymers from poly(D, L-lactide) or poly(D, L -lactide-co-glycolide) and charge-modified, hydrophilic dextrans as backbone — in-vitro degradation and controlled release of hydrophilic macromolecules. *Polymer* **39** (1998), pp. 3087–3097) for reasons of record and modified to address the amendment to the claims.

6. Li describes poly D,L lactide grafted dextran (see the entire document with emphasis on the abstract, and experimental section). Li does not disclose that the separate forms, the L-lactide grafted form of dextran and the D-lactide grafted form of dextran are combined to form the composition of claim 1. However, the combination of the L-lactide grafted form and the D-lactide grafted form of dextran reads on the D,L lactide grafted dextran. Specifically, claim 1 does not indicate any special ratios of the L-lactide dextran to the D-lactide dextran that may have provided some difference between the claimed and the disclosed. Li's disclosure of lactide grafted dextran meets the dispersible hydrophilic polymer and the dextran of claim 1. Regarding the limitation that the lactic acid in the D- or L- forms of the lactic acid has 7-25 lactic acid monomers on the average, it is noted that the artisan has the ability of using lactic acid monomers having appropriate number of lactide monomers that would lead to the desired lactide grafted polymer that would encapsulate and degrade to release hydrophilic molecules. Li prepares the lactide grafted dextran as microspheres (abstract; page 6198) meeting claim 29; the protein such as BSA (abstract and pages 3093 and 3094) that can be released from the grafted

polymer meets claims 30 and 31. Since the D,L- forms contain the D- and L-forms, one having ordinary skill in the art at the time the invention was made would have reasonable expectation that grafting the dextran with the D,L-form of the lactide or combining the D- or L-lactide grafted forms of the dextran would provide the anticipated in vitro degradation or the polymer or in vitro degradation and controlled releases of hydrophilic molecules such the degradation leads to release of protein or peptides (abstract; pages 3093, 3094, at least). While Li does not say that the microspheres formulation is a hydrogel, lactide and dextran hydrogels are known in the art and the artisan would formulate composition as a hydrogel as evidenced by the abstract, column 2, lines 6-8 of US 4,814,182. In the absence of unexpected result, a composition that comprises D, L-lactide grafted dextran that is a combination of L-lactide grafted dextran and D-lactide grafted dextran is not inventive over a D,L-lactide grafted dextran. Because the claims use the language of comprising, the D,L-lactide grafted form of the dextran meets the L-lactide and D-lactide grafted dextran.

7. Amended claim 15 and dependent claims 16, 17, 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. Li et al. ("Biodegradable brush-like polymers from poly(D, L-lactide) or poly(D, L-lactide-co-glycolide) and charge-modified, hydrophilic dextrans as backbone — synthesis, characterization and in vitro degradation properties," in *Polymer* **38** (1997), pp. 6197–6206) in view of Jarret et al. (US 4,788,979) or Bays et al. (US 4,650,488) for reasons of record and modified to address the amendment to the claims.

8. Li discloses preparation of D,L lactide grafted dextran (see the whole document with emphasis on the abstract; pages 6198, 6199, 6202, 6204). Li suggests that molecules such as peptides and proteins have been known to be delivered by lactide polymers (page 6197) meeting

claims 27 and 28. Li prepares the lactide grafted dextran using D, L-lactide and since the D,L-form contains the D- and L-forms, one having ordinary skill in the art at the time the invention was made would have reasonable expectation that grafted the dextran with the D,L-form of the lactide or combining the D- or L-lactide grafted forms of the dextran would provide the anticipated in vitro degradation or the polymer or in vitro degradation and controlled releases of hydrophilic molecules such the degradation to release of protein or peptides (abstract; pages 6193, 6194, at least). While Li is silent that the formulation is a hydrogel, lactide and dextran hydrogels are known in the art and the artisan would formulate composition as a hydrogel as evidenced by the abstract, column 2, lines 6-8 of US 4,814,182. Selection of any order of performing the process steps is prima facie obvious in the absence of new or unexpected results as it regards the sequence of steps 15 a) to 15 e). Li does not teach the use of the initiators as recited in claims 15 and 16. However, lauryl alcohol, meeting the limitation of the initiator in claims 15 and 16, is known in the art for initiating polymerization of polyesters such as lactides, glycolides and caprolactones as evidenced by column 5, line 6 of US 4,650,488 and columns 5 and 6 legends of Tables IA and B of US 4,788,979. Therefore, taking the teachings of the prior art, one having ordinary skill in the art at the time the invention was made would have reasonable expectation of success that lauryl alcohol would initiate the reaction between the lactide for grafting onto the dextran for the production of the lactide grafted dextran for the delivery of active drugs such as proteins and peptides.

Response to Arguments

9. Applicant's arguments filed 02/02/09 have been fully considered but they are not persuasive.

10. Applicant has amended claims 1 and 15. Applicant argues that reciting a mixture of dextran grafted homo-oligomers of L-lactic acid and D-lactic acid where the monomer units of the lactic acid in the homo-oligomers is patentable over the teaching of the prior art that grafts dextran to the racemic form or to the D,L-lactic acid. The examiner has carefully considered the amended claims the cited Li art and applicant's arguments. The arguments are not persuasive to overcome the rejections. In the claimed mixture is dextran grafted to D,L-forms of the lactic acid and the enantiomeric/stereospecific form is prima facie obvious over the disclosed racemic form because it is known to those skilled in the art that racemic mixtures are potentially separable/resolvable into their L- and D-isomers. Furthermore, in the present case, applicant has not provided any unexpected results from combining the D-lactic acid dextran with the L-lactic acid dextran to form a mixture. Thus, absent factual showing to the contrary, the claims are not inventive over the prior art of Li.

11. Applicant argues that Li in vol. 39 prepares microspheres and hydrogels. But while the article of Li in volume 38 of Polymer talks about preparation of microsphere, it is noted that the rejection is made under 35 USC 103 and hydrogels that are microspheres are known and specifically dextran forms hydrogel and microspheres. Furthermore, Li in Vol. 38 is silent as to hydrogels or microspheres so that since lactide and dextran hydrogels are known in the art, one would expect that either microspheres or hydrogel or hydrogel microsphere, which may all be involved in drug delivery would be expected to form and in either of the cases, hydrogel or microspheres or hydrogel microsphere, effective and desired delivery of peptides and proteins is expected to be successful. It is further noted that instant claim 29 is directed to forming the hydrogel into microspheres. Self gelling hydrogels that are based on dextran microspheres are known.

12. Applicant also argues that the office failed to provide rationale that would lead ordinary skilled artisan to combine or modify the teachings of Li, and that the separation of D.L-lactide into individual enantiomers is difficult and expensive. But, it is key to note that applicant admits that the D,L-forms are resolvable into the individual enantiomers. The resolution of racemic/racemate into enantiomers provides reasonable expectation that the enantiomeric forms are prima facie obvious over the racemic D,L-forms in view of known resolution methods for separating the racemic D,L-forms of lactic acid. See in re Adamson and Duffin, 125 USPQ 233 (CCPA 1960).

13. Applicant further argues that Li employs heating in the process of preparing the dextran polymer. But the claims do not exclude heating step; the comprising language is open. The claims have not recited that the hydrogel is formed by non-covalent stereocomplex interaction.

14. Applicant argues that the Office action failed to address the rejections in view Graham or in combination with Jarret and/or Bays. The examiner disagrees. Graham is an evidentiary reference showing that lactide and dextrans hydrogels are known; Graham was never used as art. Regarding applicant's arguments that Graham prefers chemically cross-linked synthetic hydrophilic polymers to form hydrogel, it is noted that a reference is not limited to the preferred embodiments (*in re Meinhardt*), in the same way, Graham, which discloses dextran to form hydrogel is not limited to the preferred embodiments. Li in vol. 30 of the Polymer Journal, uses dodecanol, also known as lauryl alcohol and stannous octoate as co-initiators in the synthesis of the graft polymer (see page 6199, under results and discussions). The Bays reference, US 4,650,488 was addressed as teaching that lauryl alcohol is known in the art to initiate polymerization of lactides and polyesters. Legend of Tables 1A and B of Jarret (US 4,788,979) were cited as teaching that lauryl alcohol is an initiator.

No claim is allowed.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BLESSING M. FUBARA whose telephone number is (571)272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Blessing M. Fubara/
Examiner, Art Unit 1618
/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618